REMARKS

Entry of the foregoing and favorable reconsideration and reexamination of the subject matter pursuant to and consistent with 37 C.F.R. § 1.112 is respectfully requested.

Applicant requests consideration of these additional remarks which supplement the response file on June 29, 1999. It will be demonstrated below that the current claims of record are clearly novel and unobvious over the cited prior art of record and should be taken into consideration by the Examiner.

It should be recalled that the present claims of record are directed to a method aiming at inhibiting the replication of an immunodeficiency retrovirus wherein 100% inhibition of the retrovirus in primary cultures of monocytes in the host is achieved using selected muramyl peptides.

It should be brought to the immediate attention of the Examiner that:

(1) the claims of record encompass 100% inhibition of the retrovirus which is not disclosed in the prior art; and
(2) this inhibition was demonstrated in primary cultures (cultures prepared directly from the tissues of an organism) of monocytes of the host, which is also not demonstrated in the cited prior art.

Applicant submits that the demonstration in the present invention of 100% inhibition of a retrovirus in primary cultures of monocytes is an extremely important aspect of the present invention that must be taken into

consideration by the Examiner in analyzing the prior art. This is because it is known in the art that the use of primary cultures of monocytes is a more scientifically sound *in vitro* system for testing drugs or medicaments for the inhibition of HIV-1 than in those cell lines disclosed in the prior art, as will be discussed more extensively below under the heading HIV-1 replication.

It should be emphasized, as will be discussed in greater detail below, that the cited prior art teaches the use of muramyl peptides for inhibiting HIV-1 infection using strains that are infected by T-Tropic HIV-1 strains. The prior art is silent with respect to the use of muramyl peptides for inhibiting immunodeficiency retroviruses in the presently claimed primary cultures of monocytes which are infected by M-Tropic HIV-1 strains.

HIV-1 REPLICATION

It is now known that HIV-1 needs to replicate in macrophages or dendritic cells prior to spreading to T lymphocytes. At the early stages of HIV-1 infection, shortly after seroconversion and during the asymptomatic period of AIDS, macrophage tropic or M-Tropic strains of the virus predominate.

In contrast, in the late stages of HIV-1 disease in association with CD4 T cell decline and progression to AIDS, T cell lines or T-Tropic strains of HIV-1 predominate.

The mechanism behind entry of HIV-1 gp120 at the different stages of HIV-1 disease is different. It is now known that besides binding to the CD4 receptor, interaction of the V3 loop in gp120 with a second receptor or co-receptor is required for gp120 to enter the cells. At the early stages of HIV-1 disease the co-receptor required for the gp120 to enter the macrophages

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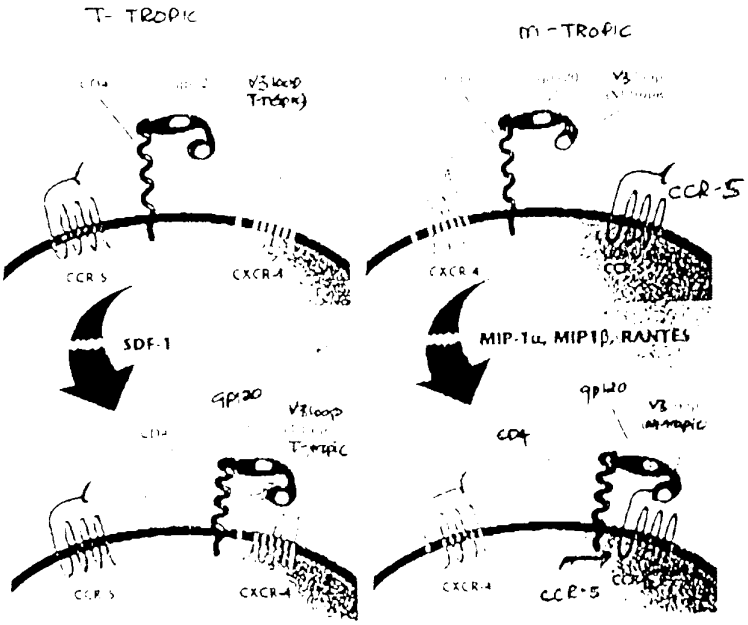
The mechanism behind entry of HIV-1 gp120 at the different stages of HIV-1 disease is different. It is now known that besides binding to the CD4 receptor, interaction of the V3 loop in gp120 with a second receptor or co-receptor is required for gp120 to enter the cells. At the early stages of HIV-1 disease the co-receptor required for the gp120 to enter the macrophages

was discovered to be the CCR-5 co-receptor. In contrast, in the late stages of the disease, the co-receptor required to enter the cells was discovered to be fusin or the CXCR-4 co-receptor. These receptors are different as can be seen schematically below:

4



Both of the co-receptors were discovered to be chemokine receptors that belong to the family of G-coupled protein receptors, which have seven transmembrane regions. The fact that these receptors have seven transmembrane regions is important, since resistance to HIV-1 infection, including T cell depletion, was discovered in certain individuals bearing a mutant alle'e of the CCR-5 chemokine co-receptor.

This mutant CCR-5 co-receptor lacks the three transmembrane segments of the wild CCR-5 receptor and was unable to support membrane fusion by both the primary and dual-tropic virus env. Hence, it was concluded that homozygous individuals having this mutant CCR-5 receptor are highly resistant to HIV-1 infection.

The above supports the theory that the CCR-5 receptor plays a primary role in the replication of HIV-1 which replication then leads in the later stages of the disease to AIDS

Hence, it is more scientifically beneficial to find drugs that target the early stages of HIV-1 infection using the M-Tropic HIV-1 strain at an early stage of infection, thus either diminuating or preventing the total onset of AIDS. This even the more so since macrophages serve as a reservoir for the virus and this reservoir is less sensitive to antiretroviral effects than T-lymphocytes.

Therefore, in the present invention inhibition of the replication of HIV-1, in the presently claimed process was demonstrated **in primary cultures of monocytes** (monocytes are precursors to macrophages) which cultures are the scientific tools of choice to use in drug evaluation experiments for HIV-1 inhibition, as explained above.

In contrast the **use of cell lines** to test for drugs which inhibit HIV-1 is highly artificial and drugs that can inhibit T-Tropic HIV replication are not necessarily effective against replication of M-Tropic viruses in macrophages. This has been demonstrated by the fact that SDF-1 (Stromal cell derived factor), the ligand for CXCR-4 , can inhibit virus entry into cell lines, but has absolutely no effect of preventing M-Tropic HIV-1 entry and infection in macrophages or primary T-lymphocytes.

Therefore, the fact that the Applicant has demonstrated 100% inhibition of a retrovirus in primary cultures of monocytes (M-Tropic HIV-1 strains) with the presently claimed muramyl peptides is an unexpected result which should distinguish clearly over the prior art of record where such a demonstration is not achieved. Rather the cited prior art teaches low inhibition of several muramyl peptides in cell lines which are T-Tropic strains of HIV-1.

These and other differences will be addressed in view of the issues brought to bear in the last Official Action.

35 U.S.C. §102(b)

The Examiner deems that Claims 14 to 21, 25, 26, 28 to 30 and 34 lack novelty in view of Schreck et al.

Furthermore, Claims 14 to 21, 25, 26, 28 to 30 and 34 lack novelty over Masihi et al.

Schreck et al.

Schreck et al. teach the use of muramyl peptides as **adjuvants** in potential vaccines against AIDS. By definition an adjuvant is an ingredient (as in a prescription or solution) that modifies the action of the principle ingredient. An adjuvant is not the active ingredient in a vaccine, as the skilled artisan well knows.

Furthermore, Schreck et al. disclose that it would be beneficial to select adjuvants that do not induce NF-κB activation and particularly if the

vaccines are to be aimed at treating seropositive individuals, since it was believed that the **activation of NF-κB purportedly enhanced HIV-1 expression**.

In fact, MDP (thr)-GDP was found **to be the only lipophilic, nonpyrogenic adjuvant that demonstrated lack of NF-κB activation**. This teaching is apparent at page 188, 2nd column, lines 13 to 15 of Schreck et al.

Although two muramyl peptides, encompassed by the present claims were tested for NF-κB activation, it was discovered that in the human Mono-Mac-6 cell line **NF-κB activation was apparent using murabutide and murametide** as set forth in the sentence bridging column 1 and column 2 at page 190 of Schreck et al. Therefore, murametide and murabutide do not belong to the selected category of an adjuvant that could be foreseen for use with an AIDS vaccine.

Furthermore, it is apparent that there is no experimental evidence that the muramyl peptides utilized in Schreck et al. can inhibit the replication of immunodeficiency retroviruses. Thus, a skilled artian can conclude nothing about whether the muramyl peptides in Schreck et al. have any inhibitory properties.

Therefore, Applicant submits that since Schreck et al. fails to teach the use of the claimed muramyl peptides as an active ingredient in a process to inhibit immunodeficiency retroviruses and since the claimed muramyl peptides do not fall into the category of those being sought in Schreck et al., the presently claimed invention is not anticipated by Schreck et al.

Masihi et al.

Masihi et al. disclose that muramyl dipeptide can enhance monocyte/macrophage CSF in serum and promote nonspecific resistance against a variety of microbial pathogens including HIV infection of $CD4^+$ H9 lymphocytes and U937 monocytic cells. However, this effect cannot be mediated by macrophage-CSF which itself has been shown to increase viral replication (see, Annex I, page 33, last paragraph, left column).

The Examiner refers to page 397 of Masihi et al. where murabutide was taught to be used as an **adjuvant** in human clinical trials. As discussed above, an adjuvant is solely used as a vehicle to modify the action of the active ingredient. Masihi et al. fails to teach that murabutide can be used in a process to treat immunodeficiency retroviruses directly.

Indeed, the cell lines used in the experiments in as the active ingredient in the manufacture of a medicament are H9, KE37/1 and U937 which are only infectable by T-Tropic HIV-1 strains. In contrast the present invention uses primary cultures of monocytes which are only infectable by M-Tropic HIV-1 strain. Thus, Masihi et al. disclose muramyl peptides for targeting the late stages of HIV-1, while the muramyl peptides in the process of the presently claimed invention target the early stage of HIV-1.

Therefore, in view of the above, Applicant submits that the presently claimed invention is not anticipated by Masihi et al.

35 U.S.C. §103(a)

Masihi et al.

Masihi et al. fail to teach the skilled artisan that murabutide can be used in a medicament as the active ingredient for inhibiting the replication of a retrovirus. Rather Masihi et al. teach the use of murabutide only as an adjuvant.

Furthermore, a skilled artisan would not extrapolate the results of a muramyl dipeptide disclosed in Masihi et al. to include all muramyl peptides, since as taught in Masihi et al. at page 189 under Reagents, different muramyl peptides have different properties.

Only if the Examiner deems that a skilled artisan would indeed extrapolate results from MDP to the rest of the muramyl peptides, Applicant would like to point out that Masihi et al. discloses only 67% reduction of the p24 antigen using MDP and only a 38% inhibition on day 14 using infected $CD4^+$ KE37/L lymphocytes and further teaches that 1000 μg/ml dosages were more effective.

Moreover, Figure 3 clearly demonstrates that less than 50% inhibition of p24 antigen using MDP at 1,000 μg/ml is achieved in U937 monocytic cells. **This percentage inhibition cannot be compared to the 100% inhibition achieved by the claimed muramyl compounds of the present invention**, which Applicant submits is an unexpected result.

Furthermore, Masihi et al. teach using 1000 μg/ml MDP which is an extremely high dosage and the side effects of MDP, including pyrogenecity and inflammatory reactions would be enormous at this particular dosage. This would discourage the skilled artisan to pursue a medicament using MDP.

Finally, in Masihi et al., the cell lines in which the muramyl peptides were tested for inhibition of HIV-1 are T-Tropic HIV-1 strains. Masihi et al. is silent with respect to the testing of these compounds in M-Tropic HIV-1 strains which clearly distinguishes the presently claimed invention from this reference, as discussed above.

In other words, Masihi et al. teach that MDP can inhibit HIV-1 infection in the late stages of the disease. Masihi et al. does not disclose nor demonstrate that MDP or any other muramyl peptide for that matter can target the early stages of HIV-1 infection, which is the most important stage to target.

It should be clear that silence in a reference is not a proper basis to maintain an obviousness rejection.

From the foregoing, favorable action in the form of a Notice of Allowance is respectfully requested and earnestly solicited.

If the Examiner has any questions concerning this application, he is requested to contact the undersigned at (703) 205-8000 in the Washington, D.C. area.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees

required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

Respectfully submitted,

BIRCH, STEWART, KOLASCH & BIRCH, LLP

By: (Signature)
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GMM/MAA/bsh

Annex I

Host factors in the pathogenesis of HIV disease

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Summary: Host factors play an important role in determining rates of disease progression in human immunodeficiency virus (HIV)-infected individuals. HIV is able to subvert the host immune system by infecting CD4+ T cells that normally orchestrate immune responses and by inducing the secretion of proinflammatory cytokines that the virus can utilize to its own reproductive advantage. The recognition that certain chemokine receptors serve as necessary co-factors for HIV entry into its target cells as well as the fact that ligands for these receptors can modulate the efficiency of HIV infection has expanded the number and scope of host factors that may impact the pathogenesis of HIV disease. This area of investigation will no doubt yield novel therapeutic strategies for intervention in HIV disease. However, caution is warranted in light of the enormous complexity of the pleiotropic cytokine and chemokine networks and the uncertainty inherent in manipulating these systems.

HIV-infected long-term non-progressors represent an excellent model to study potential host factors involved in HIV disease pathogenesis. Genetic factors certainly have a major impact on the immune responses mounted by the host. In this regard, a polymorphism in the gene for the HIV co-receptor CC chemokine receptor 5 (CCR5), which serves as a co-receptor for macrophage (M)-tropic strains of HIV, affords a high degree of protection against HIV infection in individuals homozygous for the genetic defect and some degree of protection against disease progression in HIV-infected heterozygotes. HIV-specific immune responses including cytotoxic T lymphocyte (CTL) responses and neutralizing antibody responses also appear to play salutary roles in protecting against disease progression.

Introduction

The pathogenesis of human immunodeficiency virus (HIV) disease is complex and influenced by both viral and host factors (1). The multifactorial nature of HIV disease pathogenesis is reflected in the highly variable rates of disease progression that are observed in individuals infected with HIV. The importance of host factors in modulating rates of disease progression is further underscored by the observation that even individuals who were apparently infected from a common source may experience widely variant clinical courses. [illegible] have focused recently on host factors that have been gained [illegible] virus [illegible] virus-infected cells [illegible]

...ns have confirmed earlier work that demonstrated high levels of viral replication throughout the course of HIV infection (7–9) and have greatly expanded our understanding of the dynamics of HIV replication *in vivo*. The remarkable consistency in quantitative estimates of the rate of turnover of plasma virus raises important questions regarding the observed variability in rates of disease progression. In this regard, future studies will need to address whether the rate of viral turnover varies according to stage of disease or whether it is an intrinsic characteristic of HIV infection. In either case, it is necessary to invoke host factors in order to explain the great variability in rates of clinical disease progression.

A delicate balance among a wide array of host factors likely determines the net rate of viral replication in HIV-infected individuals. Subversion of the human immune system by HIV (i.e., infection of cells that are critical components of an intact immune system, induction of the secretion of proinflammatory cytokines, and utilization of these products of immune activation for the replicative advantage of the virus) usually tips the balance in favor of the virus. The recent discovery that certain chemokine receptors (for example, CC chemokine receptor (CCR)5, CXC chemokine receptor (CXCR)4, CCR3, CCR2b, STRL33, Bonzo, and BOB) are utilized by different strains of HIV as co-factors to gain entry into cells has greatly expanded the number of candidate host factors that may influence the pathogenesis of HIV disease (10–18). The ability of the chemokine ligands of these receptors to block HIV entry into target cells and thereby tip the balance of immune control over virus replication in favor of the host is a new concept in the field of HIV pathogenesis that has major implications for potential therapeutic intervention.

Genetic factors may determine the outcome of interactions between virus and host in several ways. First, the host's HIV-specific immune responses are constrained by the individual's major histocompatibility complex (MHC) alleles. In addition, the recently discovered genetic defect in the CCR5 gene has a major impact on susceptibility to HIV infection in individuals homozygous for the defect, and on disease progression in HIV-infected individuals heterozygous for the defect. HIV-specific cellular and humoral immune responses likely play an important role in the control of viral replication, although the precise correlates of protective immunity have not been established. However, recent studies have shown that qualitative as well as quantitative features of these immune responses may be important modulators of disease progression.

Appreciation of the role of host factors in the pathogenesis of HIV disease should lead to the design of novel therapeutic strategies. The goal of tipping the balance in favor of the host over virus replication may appear to be simple, however the extraordinary complexity of manipulating host factors to this end is fraught with many potential complications. The latter point is highlighted by the negative outcomes of clinical trials for bacterial sepsis. For targeted molecules that ought to be directly involved in the pathogenesis of sepsis (for example, lipopolysaccharide, interleukin (IL)-1, and tumor necrosis factor (TNF)-α) (19), the need to consider therapeutic options in the context of a balance between pro- and anti-inflammatory mediators and the need to consider distal interactions in a complex pleiotropic cytokine network apply not only to sepsis (20), but to HIV disease as well.

Cytokines and HIV disease: dysregulation of cytokine production

A highly complex network of cytokines operates to regulate the immune system. This network is redundant and pleiotropic, and operates in an autocrine and paracrine manner to stimulate or suppress cellular proliferation and differentiation, and to modulate immune function (21). Chronic immune activation induced by HIV infection and associated opportunistic infections results in dysregulation of the cytokine network. Many of the observed alterations in cytokine production contribute to HIV pathogenesis by further stimulating viral replication, suppressing the ability of the immune system to mount a strong antiviral response, and inducing cytokine-mediated cytopathic effects (1, 22–24).

Similar to other chronic infections, HIV infection is associated with increased expression of proinflammatory cytokines, especially during the later stages of disease (25). High levels of TNF-α, IL-1β, and IL-6 are secreted by peripheral blood mononuclear cells (PBMC) (25–30) and macrophages (31–34) from HIV-infected subjects. TNF-α, IL-1β and IL-6 are also found at elevated levels in the serum (35–42), cerebrospinal fluid (43–46), and tissues (44, 47). High levels of expression of these cytokines, as well as interferon (IFN)-α (46, 47, 50), and IL-1, 3 (47, 50), are particularly evident in lymphoid tissue, a major site of HIV replication throughout the course of disease (48, 49, 51, 52). Chronically activated and expanded CD8+ T cells (47, 52) and macrophages (32, 34) are thought to be major contributors to the elevated cytokine levels observed in HIV-infected subjects.

In addition to alterations in cytokine production due to chronic immune activation, HIV-specific upregulation of certain cytokines, for example, proinflammatory cytokines can be demonstrated in PBMC [illegible]

HIV infection in vitro or after treatment with HIV proteins, such as envelope gp120 and Tat (24, 55–62).

Another major disruption in the cytokine pattern observed in HIV disease is a progressive loss in the ability to produce immunoregulatory cytokines, such as IL-2 and IL-12 (63–66). IL-2 and IL-12 are critical for effective cell-mediated immune responses, as they stimulate proliferation and lytic activity of cytotoxic T lymphocytes (CTL) and natural killer (NK) cells. These cell-mediated immune effectors represent the primary mechanism whereby most viral infections are cleared. In addition, IL-12 is essential for stimulating the production of T helper (Th)1-type cytokines, including IL-2 and IFN-γ, that favor the development of cell-mediated immune responses (67–69). While it is clear that the Th1 limb of cellular immune responses is impaired during the course of HIV infection (65, 70–73), controversy surrounds the proposed dominance of Th2-like responses (i.e. secretion of IL-4, IL-5, and IL-10) during progression of HIV disease. Clerici et al. showed that stimulated PBMC from HIV-infected patients exhibit a preferential Th2 pattern of cytokine secretion with disease progression (65, 70, 71, 74); however, other investigators have found a skewing of the cytokine secretion pattern of T cells from HIV-infected patients toward a Th0 state (i.e. secretion of cytokines characteristic of both Th1 and Th2 patterns) rather than toward a Th2 state (47, 72, 73). In either case, the finding that HIV replication is more efficient in Th0 compared to Th1 clones (72, 75) highlights the importance of impaired Th1 responses in the pathogenesis of HIV disease (76).

Effects of cytokines on HIV replication

The effects of cytokines on HIV replication were recognized in early studies wherein activated PBMC (77), macrophages (55), and B cells (79) were shown to produce soluble factors that could dramatically upregulate HIV expression in acutely and chronically infected cells of the lymphocytic and macrophage lineages. These observations led to the identification of numerous cytokines that can directly influence HIV replication in infected cells (22, 24, 80) (Fig. 1).

Cytokines that have been reported to upregulate HIV replication in vitro include IL-1β, IL-2, IL-3, IL-6, IL-7 (81), IL-12 (82, 83), IL-15 (82, 84), TNF-α, TNF-β, and the colony-stimulating factors (CSF) macrophage (M)-CSF and granulocyte macrophage (GM)-CSF (reviewed in (24)). IFN-α, IFN-β, and IL-16 (85, 86) are primarily suppressors of HIV production, whereas other cytokines, such as IL-4 (87), IL-10 (88, 89), IL-13 (87), IFN-γ, and TGF-β, reduce or enhance viral replication depending on the infected cell type and the culture condi-

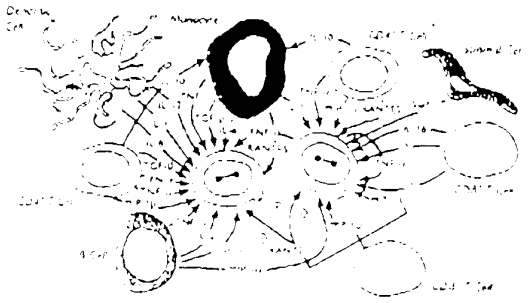


Fig. 1. Endogenous cytokines regulate viral replication in CD4+ T cells. Numerous cytokines, particularly the proinflammatory cytokines TNF-α, IL-1β, and IL-6, strongly upregulate viral replication. TGF-β and IL-10 downregulate viral replication. In the case of IL-10, this effect is in part due to downregulation of proinflammatory cytokines. The β-chemokines, which are secreted by a variety of cells, including CD8+ and CD8− noncytotoxic cells, strongly inhibit infection by M-tropic strains of HIV-1, whereas SDF-1 inhibits infection with T-tropic strains. (Adapted from (24).)

tions (22, 24, 80). Many cytokines, such as the interferons and TNF-α, can influence HIV replication in both T cells and macrophages, while others, such as M-CSF, are cell lineage-specific. The effects of a particular cytokine are often greatly influenced by the activity of other cytokines present in the microenvironment. In this regard, certain cytokines have been demonstrated to act in a synergistic (88–90, 93) or in an antagonistic (91–93) manner with other cytokines in regulating HIV replication. Finally, cytokines are pleiotropic and the overall effects of a particular cytokine on HIV replication often reflect the balance of both HIV-inducing and HIV-inhibiting activities.

Proinflammatory cytokines, particularly TNF-α, are considered the most potent HIV-inducing cytokines and their mechanism of action is relatively well understood. Both TNF-α and IL-1β activate the cellular transcription factor nuclear factor (NF)κB (94, 95), a strong inducer of HIV long terminal repeat (LTR)-mediated transcription. IL-6 alone appears to increase HIV expression primarily by a post-transcriptional mechanism; however, IL-6 can synergize with NFκB-inducing cytokines to enhance HIV transcription (90). The role of endogenous proinflammatory cytokines in the regulation of HIV replication has been demonstrated in several cellular systems in vitro. The production of HIV by macrophages or PBMC stimulated with physiologic inducers of proinflammatory cytokine production, such as bacterial endotoxin or IL-2, can be partially or nearly completely abrogated by the addition of anti-proinflammatory cytokine [illegible] macrophages and virus-producing [illegible]

such as IL-10 and TGF-β is attributable largely to their ability to inhibit the secretion of activity of HIV-inducing proinflammatory cytokines (92, 93, 96, 99). HIV production by infected T cells is sensitive to both the antiproinflammatory and the antiproliferative activity of such cytokines (D. Golerti & A.S. Fauci, unpublished data).

Although the role of proinflammatory and antiproinflammatory cytokines in the regulation of HIV replication in vivo has not been demonstrated conclusively, several lines of evidence suggest that these cytokines may be involved in regulating viral production. Administration of pentoxifylline, an inhibitor of the secretion and activity of TNF, to HIV-infected individuals was found to reduce HIV viremia in concert with a reduction in plasma levels of TNF-α (100, 101). The role of proinflammatory cytokines in maintaining steady-state levels of HIV replication is suggested by the observation that in vivo infusion of a single bolus of IL-10 to HIV-infected subjects resulted in a rapid and modest, albeit transient, decrease in plasma viremia (D. Weissman & A.S. Fauci, unpublished data). The kinetics of HIV suppression in vivo correlated with a dramatic reduction in the ability of cells from these subjects to be induced in vitro to secrete TNF-α and IL-1β. Furthermore, IL-10 has been found to inhibit acute HIV infection in severe combined immunodeficiency (SCID) mice engrafted with human fetal thymus and liver (102). The ability of IL-10 to suppress T-cell activation and proliferation likely also plays a prominent role in its ability to suppress HIV replication in vivo (103–105).

In addition to the use of immunosuppressive cytokines which may depress HIV-inducing immune responses, cytokines which stimulate T cells or antigen-presenting cells have been administered to HIV-infected subjects for a number of years. The use of cytokine-based therapies aimed at immune reconstitution in HIV disease has expanded over the past several years, particularly with the development of potent antiretroviral therapies that limit the potential for cytokine mediated increases in viral replication. In this regard administration of IL-2 to asymptomatic HIV-infected subjects receiving concomitant antiretroviral therapy results in significant and sustained increases in CD4+ T-cell numbers with no long-term effects on viremia (106–107). Similar immune reconstitution therapies are being proposed for IL-12, IL-15, and IL-15 (84, 108–115). New studies are continuing to expand the list of cytokines for use as potential immunotherapeutic agents. A particularly interesting cytokine-based immunotherapeutic approach is suggested by a recent report demonstrating that transfection of a CD4+ T cell line with DNA encoding the 131 amino acid form of IL-16 renders cells resistant to HIV-1 infection. CD8+ IL-16 (but not CD4+ IL-16) is also found to be due to interference with viral transcription (185, 86). This effect may be due to the ability of IL-16 to suppress T-cell activation (116–117). The combination of IL-2 and IL-16 is a particularly attractive option in that they synergistically enhance the expansion of CD4+ T cells (N. Baseler, personal communication).

In addition to the known HIV-suppressive factors mentioned previously, several undetermined soluble factors have been demonstrated to exert dramatic HIV-suppressive activity. Foremost among these is the elusive CD8+ cell-derived HIV suppressive factor(s). While lytic activity is an important component of CD8+ cell-mediated HIV suppression (1–8), cell-free supernatants from cultures of activated CD8+ cells and cell lines are able to dramatically inhibit HIV replication in both T cells and macrophages (119). CD8 antiviral factor (CAF), first described by Walker et al. (120–122), is non-cytolytic, suppresses HIV replication in a non-MHC-restricted manner at the level of HIV LTR transcription (123–125), and lacks identity to known cytokines (126).

A distinct group of HIV-suppressive factors secreted by CD8+ T cells was identified by Cocchi et al. (127). These investigators attributed the HIV-suppressive activity of CD8+ cells to the combined activities of certain chemoattractant cytokines (i.e. chemokines), including macrophage inflammatory protein (MIP)-1α, MIP-1β and RANTES (Regulated upon Activation, Normal T cell Expressed and Secreted). An unexplained finding in the study by Cocchi et al. was that although the combination of the β chemokines MIP-1α, MIP-1β, and RANTES potently suppressed the replication of several M-tropic HIV strains, they had virtually no effect on the replication of the T-cell line adapted (TCLA) strain, HIV-1 IIIB. Soon after this report, Feng et al. described the seven transmembrane orphan receptor fusin, previously known as LESTR and HUMSTR and currently designated CXCR4, as a co-receptor for T-cell (T)-tropic strains of HIV (128–130). In addition, three groups described a new chemokine receptor CCR5, which bound MIP-1α, MIP-1β and RANTES as its natural ligands (128–130). In light of the previous results of Cocchi et al., the obvious question that arose was was the CCR5 might function as a co-receptor for M-tropic strains of HIV. A series of papers from five different laboratories elegantly demonstrated this to be the case (131–141). Chemokine receptors that act in addition to HIV co-receptors are appealing candidates for host factors that accounts between the [illegible] chemokines (142–144). The general picture that has emerged is that M-tropic strains of HIV-1 [illegible] the more acute co-receptor CCR5, and [illegible] CXCR4. The more [illegible] MIP-1α, MIP-1β and RANTES [illegible] HIV strains [illegible] MIP-1α [illegible]

employ the α chemokine receptor, CXCR4, an interaction that is blocked by the CXCR4 ligand stromal derived factor-1 (SDF-1). Many primary T-tropic HIV isolates exhibit a broad range of CCR usage, including CXCR4 and CCR5 (132, 133). The recent discoveries of other HIV co-receptors have already made obsolete the simplistic notion that CCR5 and CXCR4 are the only important co-receptors for M- and T-tropic strains of HIV, respectively (17, 18, 134).

Numerous cell types produce a variety of chemokines (135, 136), and modulation of the production of these factors may influence HIV replication in a strain-specific manner (Fig. 1). Therefore, the overall effect of immune activation and the secretion of proinflammatory or immunoregulatory cytokines on HIV replication must now be considered in the context of potential influences on chemokine production, chemokine co-receptor expression, and the predominant viral quasispecies that is replicating in vivo. Chemokine production, induced during inflammation, is enhanced by several cytokines, including TNF-α, IL-β, and immunoregulatory cytokines, such as IL-2 and IL-15 (135, 137–139). Thus, in HIV-infected subjects in the early stages of disease, the ability of TNF-α to stimulate β-chemokine production and thereby suppress M-tropic entry may override its HIV-inducing effects, however, in individuals harboring predominantly T-tropic quasispecies in the later stages of HIV disease, only the HIV-inducing activity of TNF-α would be influential. In fact, TNF-α-mediated induction of β-chemokine secretion may actually enhance entry and replication of T-tropic strains of HIV (A. Kinter & A.S. Fauci, unpublished data) (Fig. 2).

Similarly, cytokines that modulate the expression of chemokine receptors would be expected to exert variable strain-dependent effects on HIV replication and spread. In this regard, IL-2 has been shown to upregulate the expression of the T-tropic co-receptor CCR5 (140).

The puzzling bottleneck in HIV transmission that so heavily favors emergence of M-tropic, non-syncytium-inducing (NSI) strains of virus in the new host (141, 142) may in part be due to the differential regulatory patterns of the relevant HIV co-receptors (140, 143). In this regard, CCR5 expression is predominantly seen in previously activated, memory T cells (i.e., $CD26^{low}CD45RA^{low}CD45RO^{+}$), whereas CXCR4 expression is seen in naive, unactivated cells (i.e., $CD26^{high}CD45RA^{+}CD45RO^{-}$). It is therefore plausible that the profound degree of immune activation that occurs during acute HIV infection may result in high expression of CCR5 and low expression of CXCR4 (M. Ostrowski & A.S. Fauci, unpublished data). Subsequently, co-infection with various other pathogens may differentially modulate the expression of HIV co-receptors and thereby exert selective pres-

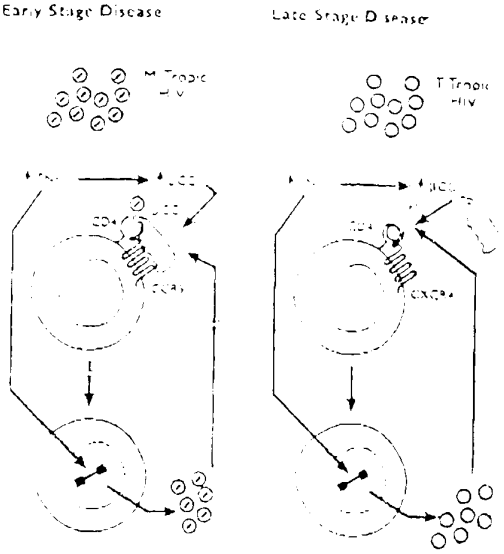


Fig. 2. Proinflammatory cytokines, such as TNF-α, have potentially dichotomous effects on HIV replication. During the early stages of HIV disease (left), M-tropic strains of the virus predominate. Although TNF-α can transcriptionally upregulate HIV expression in infected cells, at the same time it induces expression of the β-chemokines (RANTES, MIP-1α, and MIP-1β). These chemokines occupy the HIV co-receptor CCR5, blocking entry of HIV into target cells. In contrast, T-tropic strains of HIV may predominate in the late stages of HIV disease (right). In this situation, the induction of βCC by TNF-α cannot block T-tropic HIV entry via CXCR4 and in fact may enhance replication of T-tropic strains of HIV.

sure on HIV strains that use the co-receptors in question (H. Mostowski, M. Morrison, & A.S. Fauci, unpublished data).

The observation that the natural ligands of CC chemokine receptors that are utilized as HIV co-receptors act as potent inhibitors of viral entry has dramatically interrupted the known spectrum of HIV inhibitory cytokines and the mechanisms whereby they influence HIV replication. Therapeutic approaches currently being considered include administration of HIV-inhibitory chemokines, engineering antagonists that occupy HIV co-receptors without transducing a signal [144], and chemokines that are engineered to resist HIV co-receptor [illegible] particularly the regions of the viral [illegible]

PBMC from asymptomatic HIV-infected individuals harboring predominantly M-tropic HIV strains (146), but not in PBMC from individuals with more advanced disease harboring predominantly T-tropic HIV strains (146) (A. Kinter & A.S. Fauci, unpublished data). Similarly, HIV isolates obtained longitudinally from infected individuals with rapid disease progression exhibit reduced sensitivity to inhibition by β chemokines *in vitro* over time (146, 147).

A cautionary note about these potential therapies comes from the known association of the transition from M-tropic NSI to T-tropic/syncytium-inducing (SI) viruses with disease progression. The transition from an NSI to SI virus may occur by mutation of only a few amino acid residues predominantly in the envelope V3 loop (148–155). The HIV envelope V3 loop has also been shown to be a major determinant of co-receptor usage (156). Given the error rate of viral reverse transcriptase and the rapid dynamics of viral replication, mutations in the HIV envelope gene that encode SI strains must appear very early in disease; however, failure of such mutants to emerge until late in the disease process indicates a change in the selective advantage of such a mutation during the course of disease progression. Because SI variants are able to use a broader range of entry co-receptors (for example, CXCR4) compared with NSI viruses, it is possible that SI variants emerge in response to high levels of β chemokines that block cellular entry of viruses which utilize CCR5 (i.e. predominantly NSI viruses) (132, 146, 147). This potential effect of β chemokines should be investigated since the emergence of T-tropic HIV strains *in vivo* is associated with rapid CD4+ T-cell decline and disease progression (157). Further caution is warranted in light of potential dichotomous effects of the β chemokines on HIV replication in different cell types (119, 158). The situation *in vivo* is no doubt highly complex, and multiple host factors as well as regulatory aspects of co-receptor expression in different tissue compartments likely determine the environment in which selection for NSI or SI variants is made (1, 140, 159).

While *in vitro* culture systems and cell line models have allowed investigators to identify numerous host factors that influence HIV replication and to delineate the mechanisms whereby these factors suppress or enhance viral replication, it is difficult to anticipate how manipulation of these factors will ultimately influence HIV replication *in vivo*. It is clear that host factors function within the context of an interactive immune regulatory cytokine network and can have pleiotropic effects on HIV replication, some of which are viral strain-specific. Nevertheless, numerous host factors have proven or promising immunotherapeutic potential that should be further explored and pursued clinically for the treatment of HIV disease.

Immune activation

Within 6 months to 1 year following primary HIV infection, plasma viremia appears to stabilize to a steady state of set point that is a strong prognostic indicator of the rate of disease progression (1). Underlying this deceptively stable viremia is a high rate of virus production and clearance (approximately 10 billion virions daily) with virus produced by newly infected CD4+ T cells (160). Thus, even during clinically asymptomatic stages of HIV infection, persistent virus production serves as a potent source of immune activation and subsequent cytokine secretion; these activities, in turn, stimulate further viral replication.

In vitro cellular activation is essential for productive HIV infection of CD4+ T cells (161, 162), and agents that interfere with T-cell activation dramatically inhibit HIV replication in these cells (163, 164). The role of immune activation in stimulating HIV replication *in vivo* is demonstrated by increases in viremia in HIV-infected individuals persistently or transiently exposed to exogenous immune stimuli. In this regard, HIV-infected natives of sub-Saharan Africa, who experience persistent immune activation due to chronic exposure to parasites and other pathogens, harbor high viral loads associated with rapid progression of HIV disease (165, 166). Similarly, co-infection with opportunistic pathogens, such as active tuberculosis (167–170) or pneumocystis pneumonia (171), results in dramatic increases in levels of plasma HIV viremia that return to baseline upon successful treatment of the opportunistic infection (OI). The source of elevated viremia during OI was suggested by a recent study demonstrating that lymphoid tissue macrophages produce high levels of HIV in the setting of OI (172).

Confirmation of the role of immune stimulation in HIV replication has been established in studies demonstrating that immunization of HIV-infected subjects with influenza (173) or tetanus toxoid (174) antigens results in transient but substantial increases in plasma viremia. Furthermore, PBMC from HIV-infected subjects were rendered more susceptible to HIV infection *in vitro* following immunization with tetanus toxoid (174).

Long-term non-progressors: a model to study host factors in the pathogenesis of HIV disease

In recent years, [illegible] with relatively stable stages of HIV infection without [illegible] the evidence of disease progression [illegible]. Definitions of [illegible]

trary, however, a reasonable consensus definition includes documentation of HIV infection for more than 7 years, a CD4+ T cell count greater than 600 cells/μL without significant decline over time, no symptoms of HIV-induced disease, and no history of antiretroviral therapy (184). Although a minority of cases of long-term non progressive HIV infection may be associated with attenuated strains of HIV (185–189), most data suggest that viral attenuation is rare among long-term non-progressors, and that host factors play a dominant role in determining the state of non progression (180, 181, 190–192).

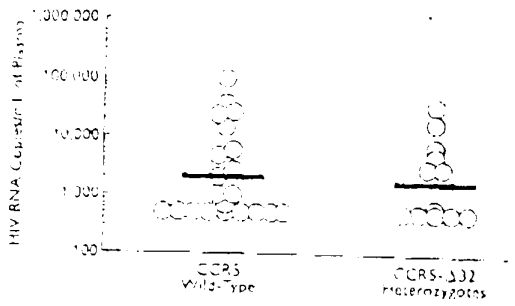


Fig. 3. Levels of plasma viremia are indistinguishable among HIV-infected long-term non-progressors stratified by CCR5 genotype. Dark bars represent geometric means

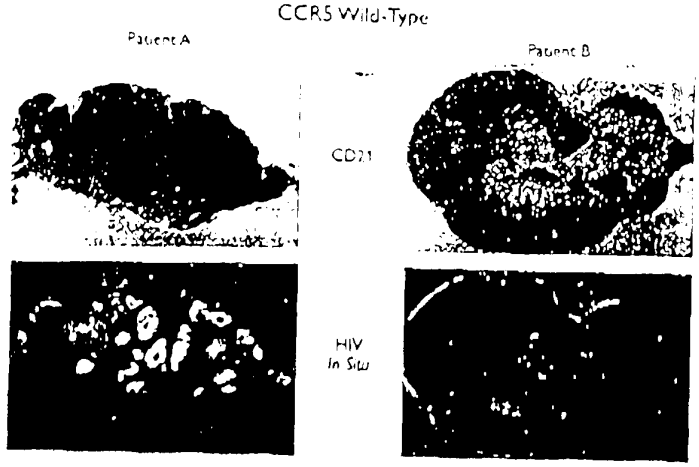
Genetic factors

Host genetic factors influence the rate of disease progression in HIV infection. A number of different mechanisms may be responsible for the observed associations between certain HLA haplotypes and different rates of HIV disease progression (193–196). The ability of certain HLA molecules to efficiently present immunodominant viral epitopes in order to generate cell-mediated immune responses may explain an association with slow disease progression. Conversely, other HLA molecules may promote immunopathogenic responses associated with more rapid disease progression. In a recent study, HLA-B27, B57, and B51 were most strongly associated with slow progression of HIV disease, while HLA-A23, B37, and B49 were associated with rapid progression (196). An HLA profile was developed that distinguished a 6-fold difference between rates of disease progression in rapid versus slow progressors. Other genetic factors linked to rates of HIV disease progression include allelic forms of the vitamin D-binding factor Gc (197), variant alleles of mannose-binding lectin (198), and the TNF α2 microsatellite allele (199).

CCR5 is a major co-receptor for M-tropic strains of HIV-1 (see above) (10–14). A mutant allele of the CCR5 gene that contains an internal 32 base pair deletion resulting in a truncated protein (200–202) has a major impact on susceptibility to HIV infection and on rates of disease progression in HIV-infected individuals. Homozygosity for the CCR5 mutation results in near-total protection from HIV-1 infection (200, 202–207). Heterozygosity for the CCR5 mutation results in decreased expression of CCR5 on the cell surface and reduced infectability of CD4+ cells with M-tropic strains of HIV-1 compared to CD4+ cells from CCR5 wild-type individuals (208). Although heterozygosity for CCR5 does not appear to afford protection against HIV-1 infection in vivo, it may confer partial protection against disease progression in HIV-infected individuals (159, 202–204, 209, 210). Protection against disease progression in CCR5 heterozygotes is due in part to the lower viral load "set point" after HIV seroconversion and a slower rate of CD4+ T-cell depletion compared with CCR5 wild-type individuals (204).

Heterozygosity for the CCR5 mutation is significantly more common in cohorts of HIV-infected long-term non-progressors compared to HIV-infected control populations (159, 202, 209, 210). However, despite the fact that the frequency of CCR5 heterozygotes is increased 2-fold among non-progressors compared to HIV-infected controls, still fewer than 50% of non-progressors are CCR5 heterozygotes (202, 209). The possibility that CCR5 heterozygotes might constitute a subgroup among non-progressors with the lowest viral loads and most preserved CD4+ T cell counts was investigated. Interestingly, CCR5 wild-type and heterozygotes long-term non progressors were indistinguishable with regard to multiple immunologic and virologic parameters of disease activity. Mean CD4+ T-cell counts were 910 cells/μL among CCR5 wild-type non-progressors and 885 cells/μL among CCR5 heterozygotes non-progressors. Geometric mean levels of plasma viremia were 2,704 HIV RNA copies/ml among CCR5 wild-type non-progressors and 1,995 HIV RNA copies/ml among CCR5 heterozygous non-progressors (209) (Fig. 3).

We have previously demonstrated that, in contrast to individuals with progressive disease, HIV-infected long-term non-progressors maintain intact lymphoid tissue architecture (180, 211). However, a great deal of heterogeneity among non-progressors is evident in the degree of lymphoid hyperplasia and viral trapping within germinal centers (see Fig. 1). When stratified according to CCR5 genotype, CCR5 wild-type and heterozygous non-progressors were [illegible] with regard to these histopathologic



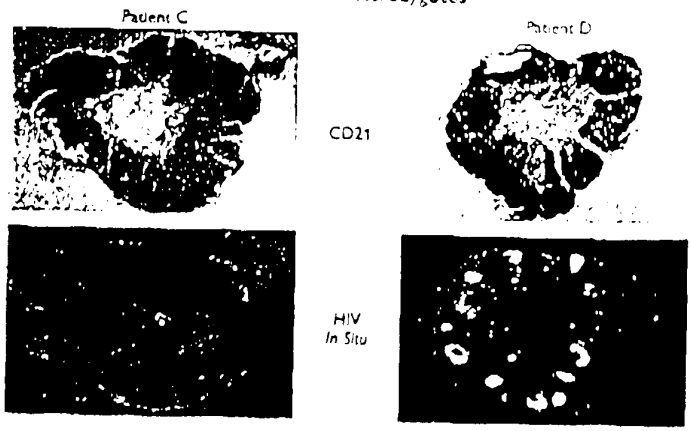


FIG. 4. The degree of follicular hyperplasia and the degree of virus trapping in lymph node germinal centers are indistinguishable among HIV-infected long-term non-progressors stratified by CCR5 genotype. CD21 staining [illegible] germinal centers [illegible] RNA in situ [illegible] hybridization [illegible] Representative lymph nodes from long-term progressors with abundant and small follicular hyperplasia and virus trapping are shown for each CCR5 genotype. [illegible]

Taken together, these data indicate that although CCR5 heterozygotes have an increased chance of becoming non-progressors, HIV-infected CCR5 wild-type individuals may arrive at the same non-progressor phenotype by other mechanisms.

Host immune response

CTL responses

HIV-specific CTL play an important role in the control, albeit incomplete, of HIV replication and spread (212, 213). High precursor frequencies of HIV-specific CTL with broad specificity have been consistently detected in long-term non-progressors compared to progressors (180, 214–217). Qualitative aspects of the HIV-specific CTL response are also important determinants of the efficacy of the CTL response in controlling viral replication. Maintenance of CTL responses specific for viral core proteins is associated with a decreased risk of disease progression (217, 218); this association does not appear to be true for CTL responses against other viral proteins. Recognition of immunodominant CTL epitopes presented by particular MHC class I alleles may result in potent anti-HIV activity (219) and may in part explain the association of certain MHC class I alleles with slower progression of HIV disease (195–196). Furthermore, the skewing of the T-cell receptor Vβ repertoire in HIV-infected patients has suggested that the ability to recruit an HIV-specific CTL response composed of a heterogeneous group of Vβ families during primary infection is associated with better control of viral replication and an improved prognosis (compared to monoclonal and oligoclonal CTL responses directed at two Vβ families (220). [illegible] This appears to be a strategy for [illegible]

of lymphocytic choriomeningitis virus that rapidly and completely mobilize the host's CTL response resulting in CTL exhaustion (i.e. high zone tolerance) (221). CTL exhaustion may occur to some degree in HIV infection where disappearance of certain originally expanded CTL clonotypes can be demonstrated in the absence of viral escape mutations that might otherwise explain the phenomenon (222).

Taken together, these observations argue against an immunopathogenic role for CTL in HIV disease (223) and in favor of a salutary role in the maintenance of low viral load and the state of non-progression. This inference is further supported by the demonstrated role of CTL in reducing levels of plasma viremia during primary HIV infection (224, 225), and the association of progression to AIDS with late viral escape from a long-lived (9–12 years) immunodominant CTL response (226).

The host CTL response against HIV is constrained by the ability of the host's MHC class I alleles to bind to various viral epitopes, while the virus is constrained by the degree to which an escape mutation impairs viral fitness. These host-virus dynamics are extraordinarily complex given the large number of permutations of viral epitopes and MHC class I alleles. Viral mutations within CTL recognition epitopes (i.e. "escape mutants") are associated with increased levels of viral replication and progression of HIV disease (226–229). Viral escape mutants may thrive due to the release of CTL control over their replication and may also inhibit CTL responses against the pre-escape viral epitope (230, 231). However, certain viral escape mutations may be costly to viral fitness. In this regard, it has been reported that diffuse infiltrative CD8 lymphocytosis in HIV infection was associated with certain HLA types that apparently constrain evolution of viral sequence diversity in the envelope V3 loop (232). Other studies have highlighted the constraints on the host CTL response imposed by MHC class I types. It has been reported that in an HIV-infected individual CTL clones specific for an HLA-B14 restricted epitope of gp41 displayed very limited diversity of T-cell receptor utilization (233). Furthermore, limited plasticity of certain CTL responses in individuals with viral escape mutants, where the dominant CTL response may remain largely directed at the pre-escape viral epitope, has been demonstrated (234, 235). The possibility that increased plasticity in the CTL response may allow the host to maintain more continuous and effective control over viral replication was suggested by studies demonstrating increased viral sequence diversity and generation of vigorous escape mutant-specific CTL responses in slow progressors (236, 237). A mathematical model of CTL virus dynamics has been proposed that describes disease progression as a result of viral sequence variation that escapes an immunodominant CTL response and shifts the host response towards a weaker epitope (238). Thus, disease progression may be the result of fitness of viral escape mutants outpacing the plasticity of the host CTL response, and slow progression may be the result of CTL plasticity overpowering viral escape mutants with limited fitness (Fig. 5).

[illegible] suppressor factor

Antiviral soluble factors elaborated by CD8+ T cells may also play a role in non-progression of HIV infection. CAF, first described by Walker et al. (120–122), is non-cytolytic and non-MHC-restricted, inhibits viral replication at the level of HIV LTR transcription (123–125), and lacks identity to known cytokines (126). CAF activity was found to correlate with stage of disease (239). Fewer CD8+ T cells from asymptomatic patients without significant CD4+ T cell depletion were required to suppress viral replication in vitro compared to CD8+ T cells from patients with advanced stage HIV disease. Studies of long-term non-progressors have demonstrated more potent CD8+ T-cell-derived soluble antiviral responses compared with progressors (131, 240).

RANTES, MIP-1α, and MIP-1β are also important antiviral soluble factors secreted by CD8+ T cells as well as other cell types (127, 145). These chemokines are natural ligands for the chemokine receptor and M-tropic HIV co-receptor CCR5 and inhibit viral replication primarily at the level of cell entry. Conflicting data have been obtained regarding a relationship between levels of these chemokines and progression of HIV disease (132, 240–245). These conflicting data are not surprising since they came from studies of sera or stimulated PBMC. A recent report does, however, support a possible role for the CC chemokines in the protection of some exposed uninfected individuals against HIV infection. Upon stimulation with HIV antigens, CD4+ T cells from these individuals secreted high levels of CC chemokines that were capable of inhibiting the replication of M-tropic strains of HIV in vitro (146). Ultimately, levels of expression of these chemokines in lymphoid tissue, the primary site of HIV replication in vivo, may be the most relevant measurement with regard to an association with rates of disease progression.

The differential chemoattractant properties of RANTES [illegible] CCR5 which attracts memory T cells [illegible] and SDF [illegible] the ligand for CXCR4 which attracts naive T cells [illegible] may influence the migration of [illegible] HIV effector [illegible] as well as potential HIV targets [illegible] [illegible] viral replication [illegible] HIV [illegible]

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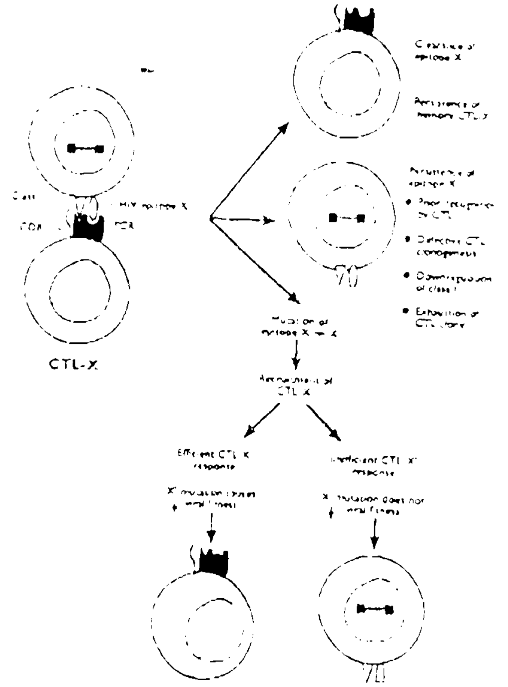

Fig. 5. The possible outcomes following CTL recognition of an HIV epitope are complex. An efficient CTL response against epitope X may result in clearance of the epitope and persistence of memory CTL (top right). Persistence of the viral epitope may be the result of a variety of factors, including poor recognition of the epitope by CTL, defective clonogenic potential of the CTL, downregulation of HLA class I molecules by viral proteins, and/or exhaustion of the CTL clone (middle right). Alternatively, a CTL escape mutation may occur in the epitope (bottom right). The outcome in this situation depends both on the relative efficiency of the CTL response directed against the escape mutant as well as on the relative cost of the mutation to viral fitness.

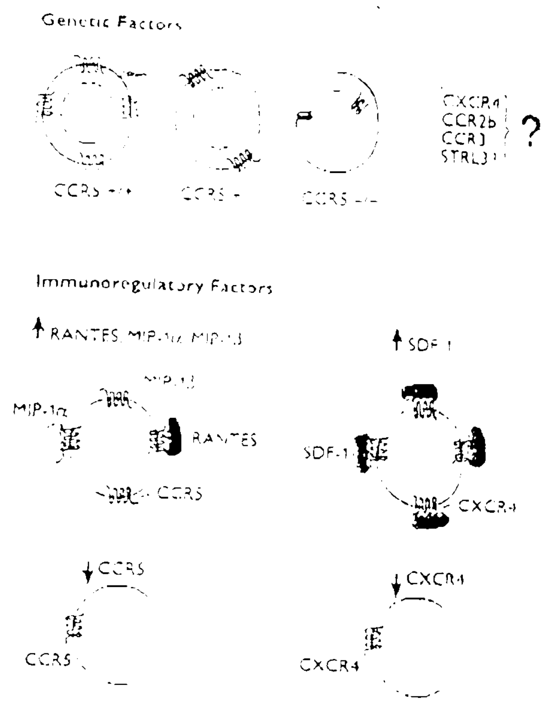

Fig. 6. Genetic as well as immunoregulatory factors govern the availability of functional HIV co-receptors. The CCR5-Δ32 allele encodes a molecule that does not function as an HIV co-receptor; individuals who are homozygous for this mutant allele are afforded near-complete protection against HIV infection, whereas heterozygotes are partially protected against disease progression. Polymorphisms in other co-receptor genes will likely also be found to correlate with rates of disease progression. Upregulation of the co-receptor ligands (RANTES, MIP-1α, and MIP-1β in the case of CCR5, and SDF-1 in the case of CXCR4) and/or downregulation of the co-receptors themselves may also limit the availability of functional HIV co-receptors.

receptors may occur by virtue of genetic polymorphisms (i.e. CCR5 Δ32) or by downregulation of their messenger RNAs or protein products (248). Alternatively, upregulation of the natural ligands of the HIV co-receptors may prevent HIV access to functional co-receptors and thereby limit infection of target cells. However, it is important to appreciate other consequences of occupancy of HIV co-receptors by their natural ligands. As noted above, high concentrations of RANTES, MIP-1α, and MIP-1β may inhibit entry and replication of M-tropic strains of HIV; however, they may also represent a selective pressure by the host immune system that may favor the emergence of T-tropic strains of HIV. Ligation of CCR5 may also result in intracellular signaling events that may actually enhance replication of T-tropic strains of HIV (A. Kinter & A. S. Fauci, unpublished data). These possibilities serve as a cautionary note to therapeutic strategies that employ chemokines or their analogues (244). Finally, IL-16 has been reported to be a soluble antiviral factor (249); however, the relationship between IL-16 production and disease progression remains to be established (130, 245).

Humoral responses

The relationship between humoral immune responses to HIV and disease progression [illegible] uncertain (250). Non-progressive HIV infection [illegible] associated with lack of [illegible] [illegible] response [illegible] [illegible] [illegible] [illegible] maintenance of high levels of p24-specific [illegible] with [illegible]

of neutralizing antibodies (254, 255). It has been reported that the presence of HIV-1IIB-neutralizing antibodies correlated with a more favorable prognosis (254). Subsequent studies demonstrated that the presence of neutralizing antibodies to primary HIV isolates and to autologous virus was associated with non-progression (255, 256). Furthermore, viral escape from neutralizing antibody responses is associated with emergence of the SI phenotype of HIV and with disease progression (255, 257). HIV-infected long-term non-progressors tend to maintain antibody responses that can neutralize a broad panel of primary isolates and also maintain neutralizing antibodies against autologous virus isolates, however, non-progressors are a heterogeneous group with regard to these neutralizing antibody responses (253, 256). Whether the maintenance of neutralizing antibodies in non-progressors is simply a marker for a relatively intact immune system or whether these antibodies play an active role in determining the state of non-progression remains unclear.

Lymphoid tissue substrate for immune competence

The morphologic abnormalities of lymphoid tissue associated with HIV disease progression are important determinants of immunodeficiency (8, 258–264). Despite the long period of HIV infection in long-term non-progressors, histopathologic examination of lymph node biopsies from these individuals revealed only mild HIV-related changes such as follicular hyperplasia (8, 20, 21), follicular involution, fibrosis and lymphocyte depletion, associated with progressive HIV disease were found to be lacking in lymph nodes from non-progressors. The degree of follicular hyperplasia seen in non-progressors is significantly lower during acute HIV progression and quantitative differences were observed in the presence of large germinal centers extending into the medullary cords (20, 21). It is likely that preservation of lymphoid architecture in non-progressors is a reflection of the lower levels of viral replication over time in these individuals. Regardless of the mechanisms responsible for lower levels of viral replication in non-progressors, preservation of lymphoid tissue architecture is a critical component of the immunocompetence observed. This further highlights the need to understand the mechanisms responsible for the destruction of lymphoid architecture during progression of HIV disease. If immunorestorative strategies in advanced HIV infection are to be successful, substrate for the generation of immune responses (i.e. intact lymphoid tissue) must be present, necessitating the prevention or reversal of the histopathologic abnormalities of lymphoid tissue associated with HIV disease progression.

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